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Factors affecting pregnancy rates in IVF patients with low ovarian reserve: the role of anti-Müllerian hormone and antral follicle count

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ABSTRACT

Aims: This study evaluated in vitro fertilization (IVF) pregnancy rates in patients with low ovarian reserve (LOR), compared pregnancy rates between patients with very low and low anti-Müllerian hormone (AMH) levels, and identified factors affecting pregnancy outcomes.

Methods: We analyzed 311 IVF cycles in 217 women with LOR. Patient selection followed the Bologna criteria for poor ovarian response. We compared the pregnant (n=22) and non-pregnant (n=289) groups for AMH, antral follicle count (AFC), oocyte parameters, and clinical outcomes. Multivariate logistic regression identified the independent predictors of pregnancy success.

Results: Pregnant patients showed higher AFC (4.6±2.4 vs 3.4±2.3, p=0.008) and AMH values (0.6±0.2 vs 0.4±0.3 ng/ml, p=0.024). Patients with AMH ≤0.5 ng/ml had higher cycle cancellation rates (26.1% vs. 4.2%, p<0.001), and clinical pregnancy rates remained similar between the AMH groups (6% vs. 8.3%, p=0.421). Multivariate analysis identified AFC (OR: 1.32, 95% CI: 1.08-1.62, p=0.007) and oocyte count (OR: 1.28, 95% CI: 1.05-1.56, p=0.015) as independent predictors of pregnancy success.

Conclusion: In our clinic, AMH levels predicted ovarian response, but not pregnancy outcomes, in patients with LOR. AFC and oocyte count were better predictors of successful IVF.

Keywords: Low ovarian reserve, anti-Müllerian hormone, infertility, pregnancy rate, in vitro fertilization

INTRODUCTION

Infertility affects approximately 15% of reproductive-age couples, and low ovarian reserve (LOR) presents a significant challenge in contemporary fertility treatment. Current data suggest that LOR accounts for nearly one-third of infertility cases among women seeking assisted reproductive technology, highlighting its growing clinical significance in reproductive medicine.[1,2] LOR, characterized by a reduced number of ovarian follicles and diminished oocyte quality, can be attributed to a range of factors including age, genetics, and environmental factors.[3] In the realm of assisted reproductive techniques, in vitro fertilization (IVF) offers hope to couples struggling with LOR, although the factors influencing successful pregnancy outcomes in these patients remain unclear.[3]

The role of anti-Müllerian hormone (AMH) in evaluating ovarian reserves has evolved significantly over the past decade. Although AMH serves as a well-established marker for assessing ovarian reserve, its predictive value for IVF success remains a subject of ongoing debate.[3,4] Recent meta-analyses have revealed that while AMH demonstrates a strong correlation with oocyte yield, its utility in predicting live birth rates appears to be limited.[5,6] Moreover, studies have shown considerable variability in pregnancy outcomes among patients with similar AMH levels, suggesting the involvement of additional factors beyond this single marker in determining reproductive success.[7]

This study aimed to evaluate IVF pregnancy rates in patients with LOR, compare pregnancy rates between patients with very low and low AMH levels, and identify the factors affecting pregnancy outcomes. Additionally, the roles of AMH and antral follicle count (AFC) in predicting IVF success were investigated.

METHODS

This study was approved by the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital

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Clinical Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-36). The research was conducted in accordance with the principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions, as well as the ethical guidelines established by the relevant institutional and national research committees.

We conducted a retrospective analysis of 217 women aged 18-40 years who underwent IVF treatment at our center between 2018 and 2020. Patient selection strictly adhered to the Bologna criteria for poor ovarian response, requiring at least two of the following features: advanced maternal age or other POR risk factors, previous poor ovarian response (≤3 oocytes with conventional stimulation), or abnormal ovarian reserve testing (AFC <7 or AMH <1.1 ng/ml).

The exclusion criteria were tubal factors, male factor infertility with a total progressive motile sperm count below 5 million, history of recurrent pregnancy loss, and presence of uterine abnormalities. All included patients underwent a thorough baseline evaluation, including hormonal assessment, transvaginal ultrasonography, and standard preoperative screening.

The diagnosis of LOR was based on serum AMH levels <1.2 ng/ml and an AFC <7, as observed on ultrasonography. AMH levels were measured using a standardized assay, and the results were used to categorize patients into two groups. AMH levels were categorized based on the commonly used threshold values in the literature.[5] Patients with AMH levels ≤0.5 ng/ml were classified as the 'very low AMH' group, while those with AMH levels >0.5 ng/ml were classified as the 'low AMH' group. This categorization was made to compare the ovarian response and pregnancy outcomes between patients with different AMH levels. The husbands' spermiograms were obtained from the hospital's urology clinic and evaluated using the WHO 2010 criteria, which assess volume, viability, sperm count, total sperm count, total progressive motile sperm count (TPMSC), morphology, pH, and viscosity.[6]

Our standardized IVF protocol included initial ovarian stimulation with gonadotropins (Merional/Gonal-f) at doses ranging from to 150-450 IU administered either intramuscularly or subcutaneously, with the starting dose determined by patient age, BMI, and previous response history. Monitoring included regular transvaginal ultrasound assessment every 2-3 days and serum estradiol measurements when clinically indicated.

GnRH antagonist (cetrotide 0.25 mg) was introduced when leading follicles reached 12–14 mm in diameter. Trigger criteria included at least two follicles ≥17 mm, with final oocyte maturation induced using Ovitrelle 250mcg. Oocyte retrieval was performed 36 h post-trigger under ultrasound guidance.

Embryology procedures followed standardized laboratory protocols, and ICSI was performed in all cases because of the limited number of oocytes. Embryo transfer was conducted under ultrasound guidance on day 2-5 based on embryo development and patient characteristics.

Statistical Analysis

Data analysis was performed using IBM SPSS v22.0. We assessed normality using the Kolmogorov-Smirnov test and applied appropriate parametric or non-parametric tests accordingly. Continuous variables were compared using the Student's t-test or Mann-Whitney U test, while categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate.

Multivariate logistic regression analysis identified independent predictors of pregnancy success, with variables showing $p<0.1$ in the univariate analysis included in the model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, with $p<0.05$. Power analysis indicated that our sample size provided 80% power to detect a 15% difference in pregnancy rates between groups.

RESULTS

Our analysis included 311 IVF cycles in 217 patients with LOR. Table 1 presents the demographic and clinical characteristics of the study population, with participants showing a mean age of 34.7±5 years, mean AMH levels of 0.48±0.3 ng/ml, and mean AFC of 3.5±2.3, representing typical characteristics of an LOR population. Initial gonadotropin doses averaged 342±103 IU, with a mean stimulation duration of 7.3±3.2 days.

Table 1. Descriptive data, laboratory and treatment results of the women participating in the study

LOR (n=311)	
	mean±SD
Age (years)	34.7±5
Duration of infertility (years)	4.7±3.6
BMI (kg/m²)	26.4±5
FSH (mIU/ml)	12.2±8.3
LH (mIU/ml)	7.3±4.5
E2 (pg/ml)	52.2±36.8
TPMSC (million)	72.3±73
AMH (ng/ml)	0.48±0.3
AFC (n)	3.5±2.3
Initial dose (IU)	342±103
Number of hMG days (n)	7.3±3.2
Total dose of gonodotropin (IU)	2887±1537
hCG day in cycle	9.4±2.2
hCG day E2 (pg/ml)	1030±708
Number of oocytes (n)	2.8±2.4
Number of MII oocytes (n)	2±2.1
Number of ICSI oocytes (n)	2±2.1
2PN (n)	1.7±1.6
Fertilization rate (%)	65.8±37.1
Embryo transfer day (day)	2.9±0.6
Number of embryos transferred (n)	1.3±0.4
B-HCG (mIU/ml)	27.3±143.2
	n (%)
IUI attempt	
Present	78/311 (25.1)
Absent	233/311 (74.9%)

Data are given as mean±SD and percentage. LOR: Low ovarian reserve, BMI: Body-mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TPMSC: Total progressive motile sperm count, AFC: Antral follicle count, AMH: Anti-Müllerian hormone, IUI: Intrauterine insemination, hMG: Human menopausal gonadotropin, hCG: Human chorionic gonadotropin, MII: Metaphase II, E2: Estradiol, ICSI: Intracytoplasmic sperm injection, OPU: Oocyte pick-up

In Table 2, a comparison between the pregnant (n=22) and non-pregnant (n=289) groups revealed significant differences across several key parameters. The pregnant group demonstrated notably higher AFC (4.6±2.4 vs 3.4±2.3, p=0.008) and AMH values (0.6±0.2 vs 0.4±0.3 ng/ml, p=0.024). Treatment outcomes also differed significantly, with successful cycles yielding higher oocyte counts (4.1±3.2 vs 2.7±2.3, p=0.003), more MII oocytes (3.5±2.8 vs 1.9±2.0, p=0.001), and increased numbers of 2PN embryos (2.6±2.3 vs 1.6±1.5, p=0.003). Table 2 also shows that the baseline FSH, LH, and estradiol levels did not differ significantly between the groups.

Table 2. Descriptive data, laboratory and treatment results of clinically pregnant (n:22 cycles) and non-pregnant women (n:289 cycles)

	Pregnancy (+) (n=22)	Pregnancy (-) (n=289)	p
	mean±SD	mean±SD	
Age (years)	35.3±4.3	34.7±5.1	0.539
Duration of marriage (years)	6.4±5.4	5±3.8	0.389
Duration of infertility (years)	5.8±4.9	4.7±3.5	0.474
BMI (kg/m^2)	26.6±6.5	26.4±4.9	0.912
IUI (n)	0.4±0.8	0.4±0.8	0.811
TPMSS (million)	89±100	71±70	0.594
Total AFC (n)	4.6±2.4	3.4±2.3	0.008
AMH (ng/ml)	0.6±0.2	0.4±0.3	**0.024**
FSH (mIU/ml)	10.4±3.9	12.4±8.6	0.765
LH (mIU/ml)	6.4±2.5	7.4±4.6	0.558
Basal E2 (pg/ml)	53.8±20	52.1±37.8	0.171
Initial dose (IU)	306±113	345±102	0.136
Number of HMG days (n)	7.1±3.8	7.4±3.2	0.716
Gonadotropin total dose (IU)	2761±1224	2896±1559	0.834
hCG day in cycle	10±1.6	9.3±2.3	0.095
hCG day E2 (pg/ml)	1585±796	996±691	**0.013**
Number of oocytes (n)	4.1±3.2	2.7±2.3	0.003
Number of MII oocytes (n)	3.5±2.8	1.9±2	**0.001**
Number of ICSI oocytes (n)	3.5±2.7	1.9±2	**0.001**
2PN (n)	2.6±2.3	1.6±1.5	**0.003**
Fertilization rate (%)	80.6±23.4	64.2±38.1	0.123
Embryo transfer day (day)	2.9±0.4	2.9±0.6	0.641
Number of embryos transferred (n)	1.5±0.5	1.3±0.4	0.073

Data are given as mean±SD and percentage. LOR: Low ovarian reserve, BMI: Body-mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TPMSS: Total progressive motile sperm count, AFS: Antral follicle count, AMH: Anti-Müllerian hormone, IUI: Intrauterine insemination, HMG: Human menopausal gonadotropin, HCG: Human chorionic gonadotropin, E2: Estradiol, ICSI: Intracytoplasmic sperm injection, OPU: Oocyte pick-up

Further stratification of outcomes by AMH level is presented in Table 3. While the very low AMH group (≤0.5 ng/ml) experienced significantly higher cycle cancellation rates compared to the low AMH group (>0.5 ng/ml) (26.1% vs 4.2%, p<0.001), those who proceeded to embryo transfer achieved comparable clinical pregnancy rates (6% vs 8.3%, p=0.421) and similar live birth rates per cycle (3.5% vs 3.4%, p=0.392). Table 3 also demonstrates that the total gonadotropin doses and stimulation duration were similar between the AMH groups.

Multivariate logistic regression analysis was performed to identify the independent predictors of pregnancy success. Table 4 presents the results. AFC and oocyte count were significant predictors of pregnancy success, with AFC showing a 32% increase in the odds of pregnancy (OR: 1.32, 95% CI: 1.08-1.62, p=0.007) and oocyte count showing a 28% increase in the odds of pregnancy (OR: 1.28, 95% CI: 1.05-1.56, p=0.015). Other variables, including AMH level and age, were not significantly associated with pregnancy outcomes.

Table 3. Descriptive data, laboratory and treatment results of very low AMH levels and low AMH levels

	AMH≤0.5 (n=165)	AMH>0.5 (n=144)	p value
	mean±SD	mean±SD	
Age (years)	35±5.2	34.5±4.7	0.454
Duration of infertility (years)	4.9±4	4.6±3.1	0.501
BMI (kg/m^2)	26.6±5	26.2±5	0.268
IUI (n)	0.2±0.7	0.5±0.8	**0.001**
TPMSS (million)	73.6±71	70.8±75	0.469
Total AFC (n)	2.6±1.9	4.5±2.4	**<0.001**
FSH (mIU/ml)	14.3±9.7	9.8±5.4	**<0.001**
LH (mIU/ml)	8.2±5.4	6.3±2.8	**<0.001**
Basal E2 (pg/ml)	51.6±38.2	53±35.2	0.447
Initial dose (IU)	352±111	330±93.1	**0.026**
Number of HMG days (n)	7.2±3.3	7.5±3.1	0.160
Gonodotropin total dose (IU)	2931±1799	2835±1163	0.931
hCG days in cycle (n)	9.1±2.5	9.6±1.9	**0.039**
hCG day E2 (pg/ml)	777.4±615.9	1307.8±702.9	**<0.001**
Number of oocytes (n)	1.9±1.6	3.6±2.7	**<0.001**
Number of MII oocytes (n)	1.4±1.3	2.6±2.5	**<0.001**
Number of ICSI oocytes (n)	1.4±1.4	2.6±2.5	**<0.001**
2PN (n)	1.5±1.1	1.9±2	0.417
Fertilization rate (%)	71.8±37.7	61.1±36.1	**0.010**
Embryo transfer day (n)	2.8±0.5	2.9±0.6	0.320
Number of embryos transferred (n)	1.2±0.4	1.3±0.5	0.400
Clinical pregnancy rate per cycle (%)	6%	8.30%	0.421
Clinical pregnancy rate per embryo transfer (%)	14%	13.40%	0.439
Live birth rate per cycle (%)	3.50%	3.40%	0.392
Live birth rate per embryo transfer (%)	8.40%	5.60%	0.240
	n (%)	n (%)	
Cycle outcome			<0.001
Cycle cancellation for lack of response	43 (26.10)	6 (4.20)	
OPU negative	8 (4.80)	4 (2.80)	
Embryo transfer	71 (43.00)	89 (61.81)	
OPU, no embryo development	43 (26.10)	45 (31.25)	

Data are given as mean±SD and percentage. LOR: Low ovarian reserve, BMI: Body-mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TPMSS: Total progressive motile sperm count, AFS: Antral follicle count, AMH: Anti-Müllerian hormone, IUI: Intrauterine insemination, hMG: Human menopausal gonadotropin, hCG: Human chorionic gonadotropin, E2: Estradiol, ICSI: Intracytoplasmic sperm injection

Table 4. Multivariate logistic regression analysis of factors affecting pregnancy success in IVF patients with low ovarian reserve

	OR	95% CI	p value
Antral follicle count	1.32	1.08-1.62	0.007
Oocyte count	1.28	1.05-1.56	0.015
AMH (ng/ml)	1.15	0.95-1.40	0.150
Age (years)	0.98	0.92-1.04	0.500

AFC: Antral follicle count, AMH: Anti-Müllerian hormone, OR: Odds ratio, CI: Confidence interval

DISCUSSION

Our findings highlight the complex relationship between ovarian reserve markers and IVF outcomes in patients with LOR. The observation that AMH effectively predicts ovarian response but not pregnancy outcomes aligns with previous studies suggesting that additional factors beyond ovarian reserve markers play a critical role in determining reproductive success.[7-9] Although AMH is a valuable tool for estimating oocyte retrieval during ovarian stimulation, its ability to predict live birth rates remains limited, as evidenced by the considerable variability in pregnancy outcomes among patients with similar AMH levels.[10,11] This discrepancy underscores the importance of integrating multiple predictive factors to assess the fertility potential.

In agreement with previous research, we found a positive correlation between the number of retrieved oocytes and live birth rate.[9] In our study, the pregnant group demonstrated significantly higher oocyte counts, AFC, and AMH levels than the non-pregnant group, reaffirming the prognostic value of these parameters in IVF outcomes. However, the predictive utility of AMH and AFC in achieving pregnancy remains a topic of debate, with some studies highlighting their limitations in directly influencing pregnancy success.[12,13]

The inconsistency in the predictive value of AMH and AFC reflects the multifaceted nature of the LOR and its impact on oocyte and embryo quality. While our findings align with those of prior studies suggesting that reduced oocyte numbers in LOR cases do not necessarily compromise oocyte or embryo quality[14], others have reported that even slight elevations in AMH levels can be associated with higher pregnancy rates.[15,16] In our study, multivariate logistic regression analysis identified AFC and oocyte count as significant predictors of pregnancy success in patients with a LOR. These findings are consistent with those of previous studies that have highlighted the importance of AFC and oocyte yield in predicting IVF outcomes.[17,18] AFC, which reflects the number of recruitable follicles, has been widely recognized as a reliable marker of ovarian reserve and the response to stimulation.[19] Similarly, a higher oocyte count has been associated with an increased chance of fertilization and embryo development, ultimately leading to higher pregnancy rates.[9] AMH, while useful in predicting ovarian response, was not significantly associated with pregnancy outcomes in our study, aligning with reports suggesting its closer relation to oocyte yield rather than embryo quality or implantation potential.[5] However, other studies have reported conflicting results, indicating that even small increases in AMH levels may be associated with higher pregnancy rates.[10] These discrepancies may be attributed to differences in patient populations, laboratory protocols, or thresholds used to define low AMH levels. In our study, age, often associated with diminished ovarian reserve, did not significantly affect pregnancy outcomes, likely due to the narrow age range of the population or the predominant role of AFC and oocyte count in determining success. Our findings underscore the importance of incorporating multiple predictive factors, including AFC and oocyte count, in the assessment of IVF success in patients with a LOR. Future studies should focus on refining stimulation protocols and optimizing laboratory conditions to improve the outcomes in this challenging patient population. These conflicting findings highlight the complexity of LOR and the need for a nuanced approach for patient assessment and treatment planning.

Notably, our study observed significant differences in cycle cancellation rates between the very low and low AMH groups, with patients in the very low AMH group (AMH ≤0.5 ng/ml) experiencing higher cancellation rates (26.1% vs. 4.2%, $p<0.001$). Despite these challenges, the clinical pregnancy rates (6% vs. 8.3%, $p=0.421$) and live birth rates per cycle (3.5% vs. 3.4%, $p=0.392$) were comparable between the two groups. This finding underscores the potential for successful pregnancies even in patients with very low AMH levels, emphasizing the importance of individualized treatment strategies.

Our results also highlight the critical need for patient counseling regarding the potential for poor treatment response and increased cycle cancellation risk in patients with low AMH levels. Optimizing IVF outcomes in LOR cases requires not only effective stimulation protocols but also improvements in laboratory conditions and embryologist expertise. Consistent with previous literature, clinical pregnancy rates in our study ranged from 7% to 15% in LOR patients, with rates of 6% for AMH ≤0.5 ng/ml and 8.3% for AMH >0.5 ng/ml.[20] However, live birth rates per cycle remained consistent across both AMH groups, underscoring the need for further research to improve the success rates in this population.

Limitations

Our study had several limitations. The retrospective design and small sample size of the pregnancy group limited the ability to establish causality and may have affected the reliability of statistical analyses. Variations in patient characteristics, such as age and infertility, could have influenced the outcomes and reduced their generalizability. Protocol changes during the study, including adjustments to gonadotropin dosing and trigger timing, may have introduced treatment inconsistencies. Moreover, the learning curve of our embryology team, as a newly established center, likely contributed to the variability in the results. Finally, this single-center study limits the broader applicability of our findings to other clinics with different patient populations and protocols.

CONCLUSION

In conclusion, AMH levels alone may not be sufficient to predict pregnancy or live birth rates, highlighting the need for a more comprehensive approach for IVF treatment planning in patients with LOR. AFC and oocyte count, along with other dynamic markers, should be incorporated into patient assessments to improve the predictive accuracy and outcomes. To address the challenges in LOR management, future studies should focus on key areas such as refining laboratory protocols and enhancing embryologists' expertise to optimize embryo development. Additionally, investigating genetic and molecular markers to improve the prediction of ovarian response, exploring metabolomic profiles of follicular fluid as novel biomarkers, and examining endometrial receptivity factors are critical steps. Personalized stimulation protocols tailored to individual patient characteristics combined with lifestyle interventions may also contribute to improved

treatment success. Integrating these parameters into a cohesive and personalized treatment framework, supported by prospective multicenter trials, holds great potential for advancing IVF planning and achieving better outcomes in this challenging patient population.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-36).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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